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# Episodic Memory Meets Working Memory in the Frontal Lobe: Functional-Neuroimaging Studies of Encoding and Retrieval

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**ABSTRACT:** Recent functional-neuroimaging studies have provided a wealth of new information suggesting that regions of the prefrontal cortex play a role in episodic memory encoding and retrieval. This review seeks to evaluate the results of these studies in the context of one general model that has proposed that the left prefrontal cortex is preferentially involved in episodic memory *encoding*, whereas the right prefrontal cortex is preferentially involved in episodic memory *retrieval*, irrespective of the type (e.g., modality) of information being remembered. The origins of this framework are considered in some detail and then all relevant functional-neuroimaging studies are critically reviewed. The results of this review fail to provide support for the functional-asymmetry model, suggesting instead that episodic memory encoding and retrieval may actually involve similar regions of the lateral prefrontal cortex when all factors relating to the type of stimulus material (i.e., modality), are appropriately controlled.

**KEY WORDS:** asymmetry model, laterality, prefrontal cortex, PET, fMRI

## I. INTRODUCTION

A common distinction made in the cognitive neuropsychology of memory is that between semantic and episodic memory.<sup>1,2</sup> The former refers to people's general knowledge of the world,<sup>3</sup> whereas the latter refers to the conscious recollection of personal experiences.<sup>2</sup> Although autobiographical memories (personally experienced episodes from one's past life) are most clearly synonymous with Tulving's original conception of episodic memory, most studies have used recall and recognition of recently studied material (or new learning) as a vehicle for investigating episodic memory.

In recent years, there has been a steady accumulation of experimental data suggesting that, in humans, the left and right prefrontal cortical regions may be asymmetrically involved in the encoding and retrieval of episodic memories. In brief, it has been suggested that the left prefrontal cortex is primarily involved in episodic memory encoding, for example, the committing to memory

of information, and the right prefrontal cortex is primarily involved in episodic memory retrieval, for example, the recalling or ephorizing of information.<sup>4-6</sup>

Most of the evidence in support of an asymmetrical involvement of the prefrontal cortical regions in episodic memory encoding and retrieval comes from functional-neuroimaging studies, in particular positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). These studies have either set out to investigate episodic memory and have provided direct evidence<sup>4-36</sup> or have investigated other cognitive functions such as speech and language and have provided indirect evidence (e.g., see Petersen et al.,<sup>37,38</sup> Demonet et al.,<sup>39</sup> and Raichle et al.<sup>40</sup>) Most of these studies have used verbal material as stimuli,<sup>4-6,8, 11-20,22,23,26,28-35,37-40</sup> although nonverbal material such as spatial patterns and faces have been used in some cases.<sup>7,9-11,20,21,25,27,32,36,41</sup> A recent review of the literature has led Nyberg et al.<sup>42</sup> to conclude that there is convincing evidence for a left-right

encoding-retrieval asymmetry in the prefrontal cortical regions irrespective of whether verbal or nonverbal material is employed.

Although recent reviews have suggested that the majority of functional-neuroimaging data is in accordance with a left-right encoding-retrieval-asymmetry framework, there are several reasons to suggest that the validity of this model needs to be further assessed. First, a number of studies have provided data that are inconsistent with the predictions of the asymmetry model. For example, some investigations have reported both right and left prefrontal activation in equivalent and different areas during episodic memory encoding or retrieval,<sup>12,26,43-48</sup> and others have reported a complete absence of frontal activation during episodic memory retrieval.<sup>7,49,50</sup> Second, despite a wealth of previous electrophysiological- and neuropsychological-memory studies in humans and nonhuman primates, none of these, to our knowledge, have provided clear support for the asymmetry model. For example, according to the model, patients with unilateral prefrontal lesions should be differentially impaired on either episodic memory encoding or retrieval depending on the side of their lesion. However, there have been a number of neuropsychological studies to suggest that this is not the case and that left and right unilateral prefrontal lesion patients are not disproportionately impaired on episodic memory encoding or retrieval, respectively.<sup>51-54</sup> Inevitably, in patient studies encoding and retrieval are confounded experimentally, although it is generally accepted that the former can be examined relatively independently of the latter by testing memory over very short intervals.<sup>55</sup> However, experiments using this technique have provided no evidence to support the left-right encoding-retrieval-asymmetry model.<sup>52,56,57</sup>

The aim of this review is to reassess the left-right encoding-retrieval model through a systematic analysis of those studies that have both provided, or failed to provide, empirical support. Since the original conception of the asymmetry model,<sup>4-6</sup> many studies of episodic memory have been conducted, providing a wealth of data for analysis. PET (positron emission tomography) and fMRI (functional magnetic resonance imaging) studies will form the main focus of this review, although a number of relevant neuropsychological studies will also be discussed. Owing to the large

number of usable studies, this review will focus on those that have specifically aimed to investigate episodic memory encoding and/or retrieval directly (for a full review, see Nyberg et al.<sup>42</sup>). Recently, numerous functional-imaging studies have sought to relate specific cognitive processes to the frontal-activation foci observed during memory encoding and/or retrieval tasks. Such processes include retrieval attempt and success,<sup>23,28,44,58-60</sup> monitoring,<sup>61,62</sup> organizational strategies,<sup>18,19</sup> and reflective processing.<sup>63,64</sup> The majority of this review will not consider all these processes in detail, but, rather, will consider the general role of the left and right frontal lobes in episodic memory encoding and retrieval, as proposed by a left-right encoding-retrieval model.<sup>42,65</sup> Undoubtedly, episodic memory involves contributions from and interactions between multiple cortical and subcortical regions although, in this article, because these regions are not central to the frontal-asymmetry model, the functional anatomy of episodic memory as it exists outside the frontal lobe will be largely ignored. However, this emphasis should not be taken to suggest that the frontal lobe is either wholly or uniquely involved in mediating episodic memory, but rather that it forms one component of an integrated memory system.

## II. METHODOLOGICAL CONSIDERATIONS

Until recently, direct investigation of the functional organization of memory processes within the human brain was limited to comparisons between groups of patients with damage to different cortical and subcortical regions.<sup>66-69</sup> In patient studies, it is not possible to establish which areas of the frontal cortex are involved in a given cognitive process with any degree of anatomical precision because the excisions are rarely confined to specific cytoarchitectonic areas. In recent years, however, functional-neuroimaging techniques such as PET and fMRI have provided a unique opportunity for assessing the relationship between patterns of cortical and subcortical activation and different aspects of cognitive processing in healthy control volunteers. The most widely used blood flow activation techniques use regional cerebral blood flow (rCBF) as an indirect index of neuronal (synaptic) activity. Using PET, rCBF is measured by determining the spatial distribution of

a positron-emitting tracer,  $^{15}\text{O}$ , throughout the brain, during a 60- to 120-second window. More recently, fMRI has been used to make functional maps of changes in cerebral venous oxygen concentration that correlate with neuronal activity. Typically, the subject performs the task of interest (e.g., a memory task), in one scan or set of scans and a control task requiring many, but not all, of the same motoric, perceptual, and cognitive components during another scan or set of scans. The imaging data are then reconstructed, smoothed, and normalized for global CBF (cerebral blood flow), which may vary between different scans. The data are then usually transformed into a standardized stereotaxic-coordinate system based on the three-dimensional atlas of Talairach and Tournoux.<sup>70</sup> The reconstructed, normalized, and transformed CBF images are then averaged across all subjects included in a particular study and subtraction images generated. These images represent the difference between the rCBF during the task of interest and that during the control task. Statistical parametric maps<sup>71,72</sup> are then generated and the stereotaxic coordinates ( $x, y, z$ ), of local maxima are calculated within the standardized stereotaxic system.

The  $x$  coordinate refers to the medial-lateral position, the  $y$  coordinate to the anterior-posterior position, and the  $z$  coordinate to the superior-inferior position. The point of origin is the anterior commissure, which is defined by the coordinates (0, 0, 0). The “Brodmann’s areas” (BA)<sup>73</sup> are subdivisions of the cerebral cortex based on cytoarchitectural observations and therefore can only be estimated from the location of the activation peaks within the standard cytoarchitectonic atlas.

### III. EARLY EVIDENCE FOR A LEFT-RIGHT ENCODING-RETRIEVAL ASYMMETRY: ORIGINS OF THE MODEL

The first direct evidence for an asymmetrical involvement of the left and right prefrontal cortex in the encoding and retrieval of memory came from three studies carried out in 1994. In one  $^{15}\text{O}$  PET study, Kapur et al.<sup>6</sup> compared “deep” with “shallow” episodic memory encoding. Healthy male subjects were scanned 6 times. During 2 scans, subjects performed baseline tasks involving responses to nonverbal stimuli whereas, during the

other 4 scans, they were required to listen to single nouns and to either (1) decide whether they contained the letter *a* (i.e. “shallow” processing) or (2) decide whether the noun was “living” (i.e., “deep” processing). Significant changes were observed in the left inferior prefrontal cortex, including areas 45, 46, 47, and 10, when blood flow during the shallow episodic memory-encoding condition was subtracted from that during the deep episodic memory-encoding condition. Because there was no significant difference in the right prefrontal cortex, the data were taken to suggest that the left prefrontal cortex might be specialized for the encoding of episodic memory.

In a second PET study, Tulving et al.<sup>4</sup> examined episodic memory retrieval or recognition of previously presented sentences. Healthy young male subjects first heard 120 auditory sentences in a prescan session. Six scans were then conducted 24 hours later in which the subjects heard new and old sentences mixed in varying proportions and were required to keep track of “odd” sentences (i.e., new ones). However, during the critical period of data acquisition, the sentences were either all new or all old. When the activation associated with the *detection* of the new sentences was subtracted from the activation associated with the *recognition* of old sentences, significant right dorsolateral prefrontal-cortex activation was observed from BA 10 through to BA 46 and 9. It is important to note that weaker activation was also observed within the left prefrontal cortex although most of this was situated in medial regions such as the cingulate sulcus. On the basis of these data, it was suggested that the right prefrontal cortex is more active than the left during episodic memory retrieval, or, in this case, recognition.

A separate investigation by Shallice et al.<sup>5</sup> into episodic memory encoding and retrieval converged upon the same conclusions as Kapur et al.<sup>6</sup> and Tulving et al.<sup>4</sup> During the encoding condition, subjects were PET-scanned while hearing rare-word categories, each paired with an exemplar from that category. During the retrieval condition, subjects were prompted with a category at a regular rate during scanning and had to recall the associated exemplar. In comparison with a passive listening-control condition, the episodic encoding condition activated the left anterior cingulate cortex extending into the left medial frontal gyrus (BA 9/10). In contrast, in comparison with a verbal-repeti-

tion-control task, the episodic memory-retrieval condition activated the right middle prefrontal cortex (BA 46/10) and the left anterior cingulate cortex (BA 32).

In summary, these three studies led to the initial suggestion that there is an asymmetrical involvement of the left and right prefrontal cortical regions in episodic memory encoding and retrieval, respectively, of verbal material (i.e., words). Within the same year, a meta-analysis of previous PET studies of related cognitive processes such as language<sup>37,40</sup> found evidence to further substantiate this suggestion.<sup>65</sup> A later review of neuroimaging studies<sup>42</sup> supported and extended this hypothesis to apply to both verbal and nonverbal material.

#### IV. EVALUATING THE MODEL: A REVIEW OF FUNCTIONAL- NEUROIMAGING STUDIES

Since the original formulation of the asymmetry model,<sup>4-6</sup> many studies of episodic memory encoding and retrieval have been conducted using a variety of different stimulus types. In general, these studies have used paradigms in which subjects were required to (1) remember a set of words, pictures, or abstract stimuli in a prescan session or during scanning itself, and then (2) to recall either the stimuli or a property associated with them (e.g., word category) during a subsequent scan. Memory retrieval usually requires that the subjects freely recall the learned stimuli (usually words) at their own pace, cued recall in which subjects are given a set of cues (or word stems) to prompt them, or recognition in which subjects are presented with single stimuli or pairs of stimuli and are required to respond to those which have been previously seen. Episodic memory encoding and retrieval have been investigated independently in some studies while, in others, both of these processes have been looked at within the same study.

In Tables 1 (encoding studies) and 2 (retrieval studies), we have attempted to provide an exhaustive list of these experiments together with brief details about the type of stimuli used; the experimental design employed; and regions within the frontal lobe that were associated with significant activity increase with respect to a control condition; and appropriate stereotaxic coordinates, where they are provided in the original text. In

Figures 1 and 2 these activation foci are plotted on a standard 3D MRI volume.

Given the predictions of the frontal-asymmetry model, one might reasonably expect the results of these functional-neuroimaging studies, when considered together, to demonstrate that episodic memory encoding and retrieval preferentially activate left and right frontal-lobe regions, respectively. Examination of the data presented in Tables 1 and 2 and in Figures 1 and 2 suggests that this is not the case; what emerges is a widely distributed pattern of activation foci across *both* hemispheres during episodic memory encoding (Fig. 1), and particularly during retrieval (Fig. 2). More specifically, although it is true that more encoding studies have activated left-hemisphere regions than right-hemisphere regions, several of these investigations have reported bilateral frontal-lobe activation<sup>25,29,41</sup> or activation in right frontal-lobe regions only.<sup>50</sup> For example, in the PET study by Owen et al.,<sup>25</sup> subjects were required to encode the locations of 8 white boxes presented sequentially on a computer screen and, subsequently, to retrieve that information by choosing between pairs of boxes presented in a similar way. Relative to the retrieval condition, the location-encoding task activated both left and right dorsolateral frontal regions (area 9/46).

Similarly, a number of functional-neuroimaging studies of both verbal retrieval,<sup>12,14,26,28,29,46,74,75</sup> and nonverbal retrieval,<sup>10,36,41</sup> have reported bilateral activation of the prefrontal cortex (see Table 2). For example, Petrides et al.<sup>26</sup> found bilateral activation of the prefrontal cortex (left BA 45 and 9/46, and right BA 9 and 9/46) on comparing free recall of learned words with word repetition. In another recent study, Andreasen et al.<sup>11</sup> investigated both short- and long-term-memory retrieval, using variations of a word-list learning task. In a long-term-memory-condition, subjects were given a list of words 1 week prior to scanning and were taught to recall them in a self-paced free-recall task. This was repeated with the same list a day prior to scanning until perfect recall was achieved. In the test condition, subjects were given a single yes-no-recognition task during scanning, which included distractor words. In a short-term condition, subjects were given another list of words, which ended just 60 seconds before an identical yes-no-recognition task during a separate scan. In a control condition, the subjects were required

**TABLE 1**  
**Neuroimaging Studies Investigating the Encoding of Episodic Memory:**

Study	Reference Task	Control Task	Area	BA	x	y	z
Brewer et al. <sup>32</sup>	Complex color photograph encoding	Activation for items remembered>familiar>forgotten	R. dorsolateral PFC	—	—	—	—
Busatto et al. <sup>33</sup>	Word memorization	Random number presentation	R. Broca's area	45	—	—	—
Cabeza et al. <sup>29</sup>	Stimuli: information encoding (word, temporal order)	Stimuli: information recognition (word, temporal order)	R. dorsolateral PFC	6	18	-6	44
			L. dorsolateral PFC	9	40	18	32
			L. dorsolateral PFC	6	-22	-6	44
			L. dorsolateral PFC	—	-46	16	32
Dolan and Fletcher <sup>30</sup>	Encoding new associations between words and their semantic categories	Encoding old associations between words and their semantic categories	R. precentral gyrus	4	—	—	—
Fernandez et al. <sup>113</sup>	Word encoding	Voxel (+) correlation with words recalled	L. precentral gyrus	4	—	—	—
Fletcher et al. <sup>17</sup>	Category-exemplar encoding	Passive listening	+	*	*	*	*
Fletcher et al. <sup>18</sup>	Encoding word list requiring maximal organization	Encoding word list requiring moderate organization	L. dorsolateral PFC	—	-36	22	30
	Encoding word list requiring moderate organization	Encoding word list requiring minimal organization	L. dorsolateral PFC	—	-34	14	22
Grady et al. <sup>20</sup>	Face encoding	Face matching	L. orbitofrontal cortex	—	—	—	—
			L. inferior PFC	—	—	—	—
			L. middle frontal gyrus	—	—	—	—
Grady et al. <sup>31</sup>	Word encoding	Picture encoding	R. middle frontal gyrus	8/9	26	38	32
	Semantic encoding	Nonsemantic/intentional learning	L. middle frontal gyrus	9	-16	48	16
	Intentional learning	Nonsemantic/semantic learning	L. cingulate gyrus	10/32	-8	44	4
			L. Superior frontal gyrus	9	-10	56	32
			L. middle frontal gyrus	10	-30	54	16
			L. middle frontal gyrus	45	-40	32	20
			L. orbitofrontal cortex	11	-24	32	-16
			L. inferior frontal cortex	45	-42	24	8
			L. orbitofrontal cortex	11	-4	38	-20
			R. anterior cingulate cortex	24	-16	32	20
			R. anterior cingulate cortex	32	—	—	—
Henson et al. <sup>48</sup>	Word and context learning	Word reading/press	R. anterior cingulate cortex	46	42	39	21
			R. middle frontal gyrus	8	33	21	51
			L. superior frontal gyrus	32	-3	21	42
			L. anterior cingulate	9	-45	15	18
			L. middle frontal gyrus	6	-39	12	51
			L. middle frontal gyrus	46	-51	27	18

TABLE 1 (continued)

Study	Reference Task	Control Task	Area	BA	x	y	z	
Iidaka et al. <sup>34</sup>	Word learning Pattern learning	Encoding control condition	L. inferior frontal gyrus	45/47	-58	18	0	
		Encoding control condition	L. middle frontal gyrus	9	-58	14	34	
	Word paired associate learning Semantic decision of words	PLS analysis	R. inferior frontal gyrus	47	56	16	-2	
			L. middle frontal gyrus	9	-52	10	34	
		Orthographic decision	L. superior frontal gyrus	10	-22	56	0	
			R. middle frontal gyrus	9	52	16	30	
			R. inferior frontal gyrus	46	46	36	18	
			L. middle frontal gyrus	8/9	-24	16	40	
			L. inferior frontal gyrus	45/46	-46	26	12	
			L. inferior frontal gyrus	45/6	-38	28	12	
Kapur, S. et al. <sup>6</sup>	Noun-pair encoding	L. middle frontal gyrus	47/10	-28	34	-4		
		L. inferior frontal gyrus - anterior	45, 46	-48	36	0		
Kapur, S. et al. <sup>77</sup>	Noun-pair encoding	L. inferior frontal gyrus - posterior	6, 44	-32	-4	32		
		Object encoding	L. anterior cingulate cortex	24,32	10	12	32	
	Word encoding	Fixation	L. dorsal frontal cortex	6/44	-47	9	34	
		Object encoding	R. dorsal frontal cortex	6/44	37	3	26	
	Face encoding Training of paired associate task Perceptual matching	Fixation	L. dorsal frontal cortex	6/44	-47	7	36	
		Paired associate task with novel stimuli	R. dorsal frontal cortex	6/44	37	3	26	
		Object (feature/location) Rn	R. middle frontal gyrus	—	39	10	39	
			L. anterior cingulate cortex	—	1	26	44	
	Klingberg and Roland <sup>50</sup>	Word encoding	Single word presentation	R. medial frontal gyrus	9/10	6	54	20
			Repeated word learning	R. superior frontal sulcus	9	28	40	32
New "and repeated" word learning		Encoding nonwords	L. anterior cingulate cortex	24/32	-6	38	0	
		Encoding nonwords	L. medial frontal gyrus	24	-6	2	36	
		Encoding nonwords	L. middle frontal cortex	9/10	-8	52	8	
		Encoding nonwords	L. inferior frontal gyrus	—	-40	20	24	
Kohler et al. <sup>36</sup>	New "and repeated" word learning	Encoding nonwords	L. inferior frontal gyrus	—	-28	20	12	
		Encoding nonwords	L. anterior cingulate	—	-24	22	20	
	New word learning	Encoding nonwords	R. anterior cingulate	14	34	16		
		Encoding nonwords	R. dorsolateral PFC	9/46	44	50	28	
		Encoding nonwords	L. frontopolar cortex	10	-44	51	-8	
		Encoding nonwords	None	None	None	None	None	
Maguire et al. <sup>115</sup>	Environment exploration	Encoding fonts	None	None	None	None		
	Deep word encoding	Random images	None	None	None	None		
McDermott et al. <sup>116</sup>	Deep word encoding	Word Rn	9	5	53	28		

Mottaghy et al. <sup>74</sup>	Encoding word pairs	Nonsense word pairs	L. superior frontal cortex	8 9/10	-15 -5	33 55	52 22
			L. medial frontal cortex	8	-17	45	46
			L. inferior frontal cortex	9 10	-3 -1	49 55	28 14
			L. anterior cingulate	47 45	-41 -51	25 23	-6 10
			R. PFC	32	8	32	28
			L. PFC	9/46	44	36	28
				8	40	20	44
				8	-32	32	44
				6	-40	8	48
Opitz et al. <sup>95</sup>	Encoding of novel sounds	Rn of novel sounds	R. posterior dorsolateral PFC	9/46	-52	28	32
			R. anterior insula	44/9	45	8	25
			L. posterior dorsolateral PFC	—	38	24	12
			L. anterior insula	44/9	-46	8	29
			L. mid-dorsolateral PFC	—	-47	24	0
			L. orbitofrontal cortex	46	-38	48	29
			L. ventrolateral PFC	11	-36	44	-15
			L. mid-dorsolateral PFC	45/47	-47	24	0
			R. mid-dorsolateral PFC	46	-32	46	23
			R. orbitofrontal cortex	9	38	29	45
			L. inferior prefrontal cortex	11	20	39	-12
				45	-38	32	5
Ragland et al. <sup>117</sup>	Word encoding	Rest condition and motor-baseline average	L. inferior frontal sulcus	—	40 <sup>a</sup>	56 <sup>a</sup>	5 <sup>a</sup>
Roland and Gulyas <sup>11</sup>	Visual-pattern learning	Rest	L. medial posterior frontal gyrus	—	41 <sup>a</sup>	11 <sup>a</sup>	53 <sup>a</sup>
			L. anterior cingulate gyrus	—	4 <sup>a</sup>	52 <sup>a</sup>	23 <sup>a</sup>
			R. superior lateral frontal gyrus	—	-6 <sup>a</sup>	82 <sup>a</sup>	6 <sup>a</sup>
			R. superior middle frontal gyrus	—	-3 <sup>a</sup>	73 <sup>a</sup>	5 <sup>a</sup>
			R. medial frontal gyrus	—	-21 <sup>a</sup>	72 <sup>a</sup>	13 <sup>a</sup>
			R. inferior frontal gyrus	—	-47 <sup>a</sup>	37 <sup>a</sup>	5 <sup>a</sup>
			R. anterior cingulate gyrus	—	-1 <sup>a</sup>	45 <sup>a</sup>	29 <sup>a</sup>
Shallice et al. <sup>5</sup>	Category-exemplar encoding	Passive listening	L. anterior cingulate cortex	32	-2	28	28
			L. middle frontal cortex	46	-32	34	8
				9/10	-22	36	20
			L. PFC	—	-4	22	28
Stern et al. <sup>118</sup>	Complex picture encoding	Single picture presentation	None	None	None	None	None

TABLE 1 (continued)

Study	Reference Task	Control Task	Area	BA	x	y	z
Wagner et al. <sup>92</sup>	Word encoding	Texture encoding	L. inferior frontal cortex	45, 47	-53	21	8
	Texture encoding	Word encoding	L. frontal operculum	44 44 47, 45 47	-52 -52 -37 -47	7 7 28 14	18 7 1 0
Wagner et al. <sup>119</sup>	Encoding of words later recalled	Encoding of words later forgotten	L. superior frontal cortex	6 9	-3 -6	14 56	57 21
			L. middle frontal cortex	8, 9 9	-28 -34	14 42	55 22
			L. orbitofrontal cortex	11	-13	56	-15
			Anterior cingulate	32	0	42	10
			R. inferior frontal cortex	45	48	28	16
			L. medial frontal cortex	10,32	-8	42	-2
			L. posterior/dorsal inferior frontal gyrus	44/6	-50	9	34
			L. anterior/ventral inferior frontal gyrus	45/47	-50	25	12
			L. operculum	47	-31	22	6

— None given.

<sup>a</sup> Talairach (1967) [AU: NOT IN REFERENCES LIST], coordinates given.

\* Same study as Shallice et al., 1994<sup>5</sup> [AU: IS CITE OK?]

R. = right hemisphere; L. = left hemisphere; PFC = prefrontal cortex; Rc = recall; Rn = recognition.

**TABLE 2**  
**Neuroimaging Studies Investigating the Retrieval of Episodic Memory**

Study	Reference Task	Control Task	Region	BA	x	y	z
Aguirre et al. <sup>76</sup>	Route Rc	Control	None	None	None	None	None
Aguirre and D'Esposito <sup>120</sup>	Location appearance Rn	Location position Rn	None	None	None	None	None
Allan et al. <sup>121</sup>	Location position Rn	Location appearance Rn	L. superior frontal gyrus	6	-23	15	67
	Stem cued word Rc (0 targets)	Word completion	R. anterior PFC	10/11	18	51	-15
			L. anterior PFC	10	-36	48	9
			R. middle frontal gyrus	8	36	6	51
			R. middle frontal gyrus	9	36	33	33
			R. anterior PFC	10	18	54	-6
Andreasen et al. <sup>11</sup>	Fragment cued word Rc (0 targets)	Word completion	R. superior frontal gyrus	9	22	42	30
	Short term memory word Rn	Word reading	R. PFC	9, 10	27	48	-13
				47/24			
			L. inferior frontal cortex	10	-27	49	-14
			R. medial frontal cortex	10	26	48	-15
				9	37	12	39
				46	30	44	10
				47	35	19	-5
				10	-25	53	-14
					-1	23	35
					-44	14	-3
Andreasen et al. <sup>12</sup>	Free recall of overlearned story	Rest	L. frontal operculum	—	44	15	0
	Free recall of learned story	Rest	R. frontal operculum	—	56	-2	18
			R. PFC	—	36	15	-4
			L. frontal operculum	—	35	10	-7
			R. frontal operculum	—	41	21	1
			R. PFC	—	37	11	6
			L. PFC	—	-36	14	-3
			R. PFC	—	38	15	-3
Andreasen et al. <sup>122</sup>	Free recall of overlearned words	Rest	L. frontal operculum	(47)	-45	17	-3
	Retrieval of past life events	Rest	R. anterior cingulate	32	3	0	55
			L. anterior cingulate	32	-2	26	1
Andreasen et al. <sup>123</sup>	Recognizing new faces	Face categorizing	L. anterior cingulate	—	28	41	-14
			R. inferior frontal cortex	—	35	37	11
			R. PFC	—	32	24	30
				—	35	20	22
				—	-24	47	-12
Blaxton et al. <sup>124</sup>	Cued word pair Rc	Nonstudied word generation	L. PFC	32	-8	40	12
			L. anterior cingulate				

TABLE 2 (continued)  
Study

Study	Reference Task	Control Task	Region	BA	x	y	z
Buckner et al. <sup>14</sup>	Remembered word fragment completion	Nonstudied word fragment completion	L. superior frontal gyrus	10	-10	54	6
			L. inferior frontal gyrus	47	-38	22	-12
	Auditory and different case word-stem cued Rc	Auditory and different letter case word generation.	L. superior frontal gyrus	10	-18	56	16
			L. orbitofrontal cortex	11	-16	54	-12
			R. superior frontal gyrus	10	22	52	0
			R. middle frontal gyrus	46	36	22	24
			R. anterior PFC	10	32	50	6
			R. PFC	8/9	44	18	39
			R. PFC	9	30	29	34
			L. PFC	8/9	-36	19	40
Buckner et al. <sup>11,2</sup>	Cued word Rc	Word repetition	R. PFC	8	14	29	43
			L. anterior cingulate cortex	—	-5	17	34
Buckner et al. <sup>15</sup>	Word Rn (deep and shallow encoded words)	Fixation	L. anterior insular cortex	—	-3	31	22
			R. anterior PFC	—	31	15	2
			R. anterior PFC	—	27	49	16
			R. PFC	—	29	59	-8
			R. PFC	—	39	23	28
			Medial frontal cortex	—	-3	29	-6
			R. anterior cingulate/SMA	32/6	12	16	46
			R. dorsal PFC	44	40	9	31
			R. anterior operculum	44/45/13	31	25	9
			Buckner et al. <sup>16</sup>	Word Rn (correct recognition and rejection)	Fixation	R. anterior PFC	9
R. anterior PFC	10	37				59	12
L. dorsal PFC	44/9	-37				6	34
L. anterior operculum	44/45/13	-28				19	6
L. PFC	9	-50				22	34
R. dorsolateral PFC	—	—				—	—
L. dorsolateral PFC	—	—				—	—
R. anterior PFC	10	—				—	—
L. anterior PFC	10	—				—	—
Busatto et al. <sup>33</sup> Cabeza et al. <sup>29</sup>	Word Rn Cued Rc	Word reading/press Word-pair reading				L. dorsolateral pfc	46
			L. anterior cingulate cortex	32	-8	22	32
Cabeza et al. <sup>6</sup>	Word-pair Rn Stem cued Rc/Associative Item Rn/Context Rn	Word-pair reading Item Rn/Context Rn Stem cued Rc/Associative	L. orbitofrontal cortex	11/47	-18	14	-20
			R. PFC	45	44	16	20
			R. anterior cingulate cortex	32	6	36	24
			L. pfc	45/46	—	—	—
			R. pfc	9, 46/10	—	—	—

Study	Reference Task	Control Task	Region	BA	x	y	z
Duzel et al. <sup>125</sup>	Episodic word Rn	Episodic word Rn	R. anterior pfc	10	22	56	-4
Fink et al. <sup>126</sup>	Impersonal autobiographical Rc	Semantic judgments	None	none	none	none	None
	Personal autobiographical Rc	Rest	R. dorsal/superior frontal cortex	6	4	8	60
	Personal autobiographical Rc	Impersonal autobiographical Rc	R. anterior insula	-	28	18	-4
Fletcher et al. <sup>17</sup>	Category-exemplar Rc	Word repetition	+	+	+	+	+
Fletcher et al. <sup>127</sup>	Imageable word-pair Rc	Nonimageable word-pair Rc	L. anterior cingulate cortex	—	-12	38	0
	Nonimageable word-pair Rc	Imageable word-pair Rc	L. pfc	—	-54	20	12
Fletcher et al. <sup>19</sup>	Internally cued Rc	Externally cued Rc	R. dorsolateral pfc	9/46	36	42	32
	Externally cued Rc	Internally cued Rc	R. ventrolateral pfc	45	22	8	0
					36	18	0
					32	24	8
	Internally cued Rc	Word repetition	R. dorsolateral pfc	9/46	36	44	24
	Externally cued Rc	Word repetition	R. ventrolateral pfc	45	52	18	20
			R. dorsolateral pfc	9/46	38	38	24
			R. ventrolateral pfc	45	38	12	0
			R. anterior cingulate cortex	24	6	24	16
Fuji et al. <sup>128</sup>	Repeat old words	Repeat new words	R. orbitofrontal gyrus	11	8	14	-19
			L. inferior frontal gyrus	45	-41	35	10
				44	-48	13	18
				11/47	20	40	-16
Haxby et al. <sup>10</sup>	Face Rn	Face matching	R. orbital and inferior frontal cortex				
			R. mid and inferior frontal cortex	9/45	40	24	20
			R. midfrontal cortex	46	30	44	8
			L. midfrontal cortex	8/9	-30	44	8
			L. orbitofrontal cortex	24/32	-31	35	30
			orbito frontal/anterior cingulate cortex	32	-2	20	4
			R. inferior frontal cortex	45	0	36	-4
Haxby et al. <sup>9</sup>	Face Rn	Face matching		46	—	—	—
				46	—	—	—
				10	—	—	—
Henson et al. <sup>47</sup>	Judgment of recollecting [AU: QUALIFIER NEED? SUCH AS "OLD"]word	Judgment of new word	L. inferior frontal gyrus	47	51	21	-6
			L. middle frontal gyrus	9	-54	24	33
			L. superior frontal gyrus	46	-60	27	21
				10	-12	63	18
TABLE 2 (continued)	Reference Task	Control Task	Region	BA	x	y	z

	Judgment of new word	Judgment of recollecting <small>[AU: QUALIFIER?]<sub>word</sub></small>	9	-6	39	27
	Judgment of familiar word	Judgment of new word	8	30	39	48
			6	18	6	54
			47	-51	15	-6
			9	42	21	33
			46	51	39	21
			9	—	—	—
			47	-51	15	-6
			9	-60	24	15
			9	-9	42	24
			8	18	54	42
			32	6	36	27
			8	45	18	45
			46	48	27	24
			47	36	24	-12
			9	-51	24	30
			45	-42	15	21
			32	6	36	27
			46	48	30	21
			8	33	24	48
			47	36	24	-9
			11	36	51	-12
			32	—	—	—
			46	-48	27	27
			8	-30	27	51
			47	-30	24	-6
			11	-42	45	-6
			47	38	17	-13
			8	-3	25	48
			9	-43	19	26
			47	-44	28	-8
			—	—	—	—
			32	2	36	20
			10	22	44	20
			10	22	42	-8
			10	-10	48	4
			45	44	14	4
			47	-30	20	4
			32	8	12	44
			45	44	14	4
			10	26	38	-4
			9	-43	19	26
			47	-44	28	-8
			—	—	—	—
			32	2	36	20
			10	22	44	20
			10	22	42	-8
			10	-10	48	4
			45	44	14	4
			47	-30	20	4
			32	8	12	44
			45	44	14	4
			10	26	38	-4
			9	-43	19	26
			47	-44	28	-8
			—	—	—	—
			32	2	36	20
			10	22	44	20
			10	22	42	-8
			10	-10	48	4
			45	44	14	4
			47	-30	20	4
			32	8	12	44
			45	44	14	4
			10	26	38	-4
			9	-43	19	26
			47	-44	28	-8
			—	—	—	—
			32	2	36	20
			10	22	44	20
			10	22	42	-8
			10	-10	48	4
			45	44	14	4
			47	-30	20	4
			32	8	12	44
			45	44	14	4
			10	26	38	-4
			9	-43	19	26
			47	-44	28	-8
			—	—	—	—
			32	2	36	20
			10	22	44	20
			10	22	42	-8
			10	-10	48	4
			45	44	14	4
			47	-30	20	4
			32	8	12	44
			45	44	14	4
			10	26	38	-4
			9	-43	19	26
			47	-44	28	-8
			—	—	—	—
			32	2	36	20
			10	22	44	20
			10	22	42	-8
			10	-10	48	4
			45	44	14	4
			47	-30	20	4
			32	8	12	44
			45	44	14	4
			10	26	38	-4
			9	-43	19	26
			47	-44	28	-8
			—	—	—	—
			32	2	36	20
			10	22	44	20
			10	22	42	-8
			10	-10	48	4
			45	44	14	4
			47	-30	20	4
			32	8	12	44
			45	44	14	4
			10	26	38	-4
			9	-43	19	26
			47	-44	28	-8
			—	—	—	—
			32	2	36	20
			10	22	44	20
			10	22	42	-8
			10	-10	48	4
			45	44	14	4
			47	-30	20	4
			32	8	12	44
			45	44	14	4
			10	26	38	-4
			9	-43	19	26
			47	-44	28	-8
			—	—	—	—
			32	2	36	20
			10	22	44	20
			10	22	42	-8
			10	-10	48	4
			45	44	14	4
			47	-30	20	4
			32	8	12	44
			45	44	14	4
			10	26	38	-4
			9	-43	19	26
			47	-44	28	-8
			—	—	—	—
			32	2	36	20
			10	22	44	20
			10	22	42	-8
			10	-10	48	4
			45	44	14	4
			47	-30	20	4
			32	8	12	44
			45	44	14	4
			10	26	38	-4
			9	-43	19	26
			47	-44	28	-8
			—	—	—	—
			32	2	36	20
			10	22	44	20
			10	22	42	-8
			10	-10	48	4
			45	44	14	4
			47	-30	20	4
			32	8	12	44
			45	44	14	4
			10	26	38	-4
			9	-43	19	26
			47	-44	28	-8
			—	—	—	—
			32	2	36	20
			10	22	44	20
			10	22	42	-8
			10	-10	48	4
			45	44	14	4
			47	-30	20	4
			32	8	12	44
			45	44	14	4
			10	26	38	-4
			9	-43	19	26
			47	-44	28	-8
			—	—	—	—
			32	2	36	20
			10	22	44	20
			10	22	42	-8
			10	-10	48	4
			45	44	14	4
			47	-30	20	4
			32	8	12	44
			45	44	14	4
			10	26	38	-4
			9	-43	19	26
			47	-44	28	-8
			—	—	—	—
			32	2	36	20
			10	22	44	20
			10	22	42	-8
			10	-10	48	4
			45	44	14	4
			47	-30	20	4
			32	8	12	44
			45	44	14	4
			10	26	38	-4
			9	-43	19	26
			47	-44	28	-8
			—	—	—	—
			32	2	36	20
			10	22	44	20
			10	22	42	-8
			10	-10	48	4
			45	44	14	4
			47	-30	20	4
			32	8	12	44
			45	44	14	4
			10	26	38	-4
			9	-43	19	26
			47	-44	28	-8
			—	—	—	—
			32	2	36	20
			10	22	44	20
			10	22	42	-8
			10	-10	48	4
			45	44	14	4
			47	-30	20	4
			32	8	12	44
			45	44	14	4
			10	26	38	-4
			9	-43	19	26
			47	-44	28	-8
			—	—	—	—
			32	2	36	20
			10	22	44	20
			10	22	42	-8
			10	-10	48	4
			45	44	14	4
			47	-30	20	4
			32	8	12	44
			45	44	14	4

Jones-Gottman et al. <sup>130</sup>	Odor Rn	No-odor inhalation	L. anterior insula	9	44	28	32
Kapur, S. et al. <sup>44</sup>	Word retrieval	Living/nonliving decision	—	47	-30	22	0
Kapur, N. et al. <sup>7</sup>	Face Rn	Face gender decision	R. frontopolar cortex	—	—	—	—
Klingberg and Roland <sup>50</sup>	Paired associate task after training	Paired associate task with novel stimuli	R. middle frontal gyrus	10	20	52	8
Kohler et al. <sup>36</sup>	Object (feature/location) Rn	Perceptual matching	R. middle frontal gyrus	46	32	52	16
			L. frontopolar	9	36	18	32
			Middle anterior cingulate	10	-28	52	8
			None	8/32	0	26	40
			None	None	None	None	None
			None	None	None	None	None
			R. middle frontal gyrus	10	30	58	20
				46/9	42	32	28
				6	30	2	48
			R. inferior frontal gyrus	44	46	12	20
			R. medial frontal gyrus	6	6	16	44
			L. middle frontal gyrus	10/6	-30	46	20
			L. inferior frontal gyrus	9/44	-44	14	32
			L. medial frontal gyrus	6	-6	10	44
			None	None	None	None	None
Krause et al. <sup>131</sup>	Cued Rc visually encoded imaginable words	Nonsense word presentation	None	None	None	None	None
	Cued Rc visually encoded abstract words	Nonsense word presentation	L. anterior cingulate	24	6	26	28
	Cued Rc verbally encoded imaginable words	Nonsense word presentation	L. PFC	10/46	-24	54	4
	Cued Rc verbally encoded abstract words	Nonsense word presentation	L. PFC	10/46	-20	38	16
	Cued Rc verbally encoded abstract words	Nonsense word presentation	R. PFC	10/46	42	30	36
	Font Rn	Nonword Rn	L. PFC	46	-42	18	20
	Nonword Rn	Font Rn	L. PFC	46	-22	38	16
Lee et al. <sup>94</sup>			R. orbitofrontal cortex	18	18	54	-12
			R. dorsolateral PFC	9	60	24	28
				9	18	40	36
			L. orbitofrontal cortex	11	-26	22	-8
			L. ventrolateral PFC	47	-54	20	0
			L. inferior frontal cortex	44	-56	8	16
			L. superior frontal gyrus	10	-22	52	22
Maguire et al. <sup>132</sup>	Route Rc	Follow arrows	R. middle frontal cortex	9/46	41	31	30
McDermott et al. <sup>116</sup>	Word Rn	Deep word encoding		10	37	51	22
			R. inferior frontal cortex	45/47	31	21	2
			L. middle frontal cortex	10/46	-41	49	4
				BA	x	y	z
			Region				
			Control Task				
			Reference Task				

**TABLE 2 (continued)**  
Study

McDermott et al. <sup>93</sup>	Word Rn	Face Rn	L. posterior inferior frontal gyrus	6/44	-43	5	28
			L. ventral inferior frontal cortex	—	—	—	—
			R. posterior inferior frontal gyrus	6/44	45	1	32
Moscovitch et al. <sup>21</sup>	Object identity Rn Object location Rn	Object matching Object matching	R. inferior midfrontal cortex	44,46	36	22	24
			R. inferior midfrontal cortex	44,45	34	32	16
			R. inferior midfrontal cortex	46	36	22	24
Mottaghy et al. <sup>74</sup>	Cued word Rc	Single nonsense words	R. anterior cingulate	32	8	40	16
			R. PFC	44/46	36	4	32
			L. PFC	45	-56	24	20
				9/46	-52	36	24
				47	-48	24	-12
Nolde et al. <sup>63</sup>	Picture/Word Rn	Fixation (no group analysis)	R. anterior PFC	10	—	—	—
			R. superior frontal gyrus	8	—	—	—
			R. dorsolateral PFC	9/46	—	—	—
			R. ventrolateral PFC	47	—	—	—
			L. anterior PFC	10	—	—	—
			L. dorsolateral PFC	9/46	—	—	—
			L. ventrolateral PFC	47	—	—	—
			R. PFC	45	28	30	8
Nyberg et al. <sup>23</sup>	Learned word (based on voice encoding) Rn	Word reading	L. anterior cingulate cortex	24/32	-10	18	28
	Learned word (based on semantic encoding) Rn	Word reading	R. PFC	45	28	24	8
	Novel word Rn	Word reading	L. anterior cingulate cortex	24/32	-16	20	28
			R. PFC	45	28	24	8
			L. anterior cingulate cortex	24/32	-10	18	28
			R. inferior frontal gyrus	47	34	28	4
				8	30	28	4
			L. middle frontal gyrus	—	-30	30	40
				—	-30	30	40
			L. anterior cingulate	24/32	-2	2	40
			Midline anterior cingulate	24/32	0	4	40
Opitz et al. <sup>95</sup>	Rn of novel sounds	Encoding of novel sounds	R. posterior dorsolateral PFC	44/9	45	9	30
			R. anterior insula	—	30	19	7
			L. posterior dorsolateral PFC	44/9	-46	6	33
			L. anterior insula	—	-33	19	7
			R. medial frontal cortex	9	5	48	27
Owen et al. <sup>25</sup>	Object-location Rn	Object-location encoding	R. orbitofrontal cortex	11	36	29	-20
			R. ventromedial PFC	47/11	24	24	-5
			R. middorsolateral PFC	9	44	25	29
			R. ventrolateral PFC	45/47/44	-33	19	7

Petrides et al. <sup>26</sup>	Cued word Rc	Word repetition	9/46	48	30	35	
	Free learned word Rc	Word repetition	11	20	48	-8	
				9/46	43	32	38
	R. dorsolateral frontal cortex			9	36	51	33
		R. anterior cingulate cortex		32	4	17	44
		L. midventrolateral frontal cortex		45	-23	25	3
		L. middorsolateral frontal cortex		9/46	-40	49	26
	Ragland et al. <sup>117</sup>	Word Rn	Rest condition +	10	41	41	9
				9	36	51	33
			motor baseline average	32	4	17	44
Roland et al. <sup>27</sup>	Word Rn	Word encoding	45	-23	25	3	
	Visual pattern Rn	Visual pattern encoding	9	15	24	33	
		Superior frontal sulcus	—	—	—	—	
Roland and Gulyas <sup>41</sup> [AU: NOT IN REF LIST]	Visual pattern recall	Rest	—	—	—	—	
		Frontal eye fields	—	—	—	—	
		L. medial superior frontal gyrus	—	8 <sup>a</sup>	16 <sup>a</sup>	61 <sup>a</sup>	
		L. superior frontal sulcus	—	18 <sup>a</sup>	72 <sup>a</sup>	19 <sup>a</sup>	
		L. medial frontal sulcus	—	40 <sup>a</sup>	32 <sup>a</sup>	42 <sup>a</sup>	
		L. inferior frontal sulcus	—	37 <sup>a</sup>	27 <sup>a</sup>	34 <sup>a</sup>	
		R. lateral superior frontal gyrus	—	-22 <sup>a</sup>	80 <sup>a</sup>	6 <sup>a</sup>	
		R. superior frontal sulcus	—	-19 <sup>a</sup>	47 <sup>a</sup>	44 <sup>a</sup>	
		R. medial frontal gyrus	—	-24 <sup>a</sup>	64 <sup>a</sup>	33 <sup>a</sup>	
		R. inferior frontal sulcus	—	-38 <sup>a</sup>	36 <sup>a</sup>	42 <sup>a</sup>	
		R. anterior cingulate gyrus	—	-2 <sup>a</sup>	45 <sup>a</sup>	29 <sup>a</sup>	
		L. superior lateral frontal gyrus	—	3 <sup>a</sup>	28 <sup>a</sup>	55 <sup>a</sup>	
		L. posterior middle frontal gyrus	—	40 <sup>a</sup>	14 <sup>a</sup>	45 <sup>a</sup>	
		R. medial superior frontal gyrus	—	-3 <sup>a</sup>	52 <sup>a</sup>	53 <sup>a</sup>	
		R. medial frontal gyrus	—	-38 <sup>a</sup>	29 <sup>a</sup>	41 <sup>a</sup>	
	R. inferior frontal sulcus	—	-36 <sup>a</sup>	27 <sup>a</sup>	40 <sup>a</sup>		
	R. inferior frontal gyrus	—	-37 <sup>a</sup>	29 <sup>a</sup>	33 <sup>a</sup>		
	R. inferior frontal operculum	—	-29 <sup>a</sup>	46 <sup>a</sup>	6 <sup>a</sup>		
<b>TABLE 2 (continued)</b>	<b>Reference Task</b>	<b>Control Task</b>	<b>BA</b>	<b>x</b>	<b>y</b>	<b>z</b>	
<b>Study</b>	<b>Word Rn</b>	<b>Perceptual task</b>	<b>10/46</b>	<b>38</b>	<b>48</b>	<b>8</b>	
Rugg et al. <sup>28</sup>	Word Rn	Perceptual task	10/46	38	48	8	

Rugg et al. <sup>58</sup>	Intentional Rn	Incidental Rn	46/9	42	22	28
	deep encoded words	deep encoded words	10	-30	46	-4
	Intentional Rn	Incidental Rn	32/8	4	20	48
	shallow encoded words	shallow encoded words	44	-54	14	16
	Intentional Rn	Intentional Rn	9	-42	28	32
	deep encoded words	shallow encoded words	10	24	50	8
			46/9	40	32	24
			32	-6	34	-8
			9	-46	16	36
			44	-52	18	16
Rugg et al. <sup>59</sup>	Word Rn (high density)	Word Rn (0 density)	10	-6	42	36
	Word cued Rc (high density)	Word cued Rc (0 density)	None	None	None	None
	Word cued Rc (low density)	Word cued Rc (high density)	10	32	50	18
	Possible object Rn (old items)	Possible object Rn (new items)	None	None	None	None
	Impossible object Rn (old items)	Impossible object Rn (new items)	10	-22	46	12
	Rc of less familiar words	Rc of highly familiar words	10	22	44	-6
	Rc of less familiar words	Word completion	10, 44-46	—	—	—
			None	None	None	None
			None	None	None	None
			None	None	None	None
Schacter et al. <sup>49</sup>	Possible object Rn (old items)	Possible object Rn (new items)	10/46	-31	43	8
	Impossible object Rn (old items)	Impossible object Rn (new items)	32	-7	15	32
	Rc of less familiar words	Rc of highly familiar words	11	5	35	-12
	Rc of less familiar words	Word completion	32	7	34	0
			10	-35	54	8
			10	30	46	8
			9	12	47	28
			—	0	25	43
			—	6	28	34
			—	34	56	18
Schacter et al. <sup>46</sup>			—	34	59	0
			—	-28	56	18
			—	50	19	0
			—	-28	25	3
			—	-43	16	6
			32	-2	18	36
			47	26	18	0
			10/46	18	28	24
			—	-33 <sup>a</sup>	59 <sup>a</sup>	6 <sup>a</sup>
			32	1	12	43
Schacter et al. <sup>133</sup>	True and false word Rn	Visual fixation	6	30	5	45
			10	20	52	8
			46	32	52	16
			36	36	18	32
Shallice et al. <sup>5</sup>	Category-exemplar Rc	Word repetition				
Squire et al. <sup>8</sup>	Word-stem cued Rc	Word-stem completion				
	Recognition of words	Encoding words				
Taylor et al. <sup>134</sup>						
Tulving et al. <sup>4</sup>	Word Rn	Semantic decision of words				

Tulving et al. <sup>43</sup>	Learned picture Rn	Novel picture Rn	L. frontopolar cortex	10	-28	52	8	
			Midline anterior cingulate	8/32	0	26	40	
			L. medial frontal cortex	—	-5	17	34	
			L. anterior cingulate cortex	—	-3	31	22	
			L. anterior insular cortex	—	31	15	2	
	Tulving et al. <sup>45</sup> Wagner et al. <sup>92</sup>	Learned picture Rn	Novel picture Rn	R. anterior PFC	—	27	49	16
				R. PFC	—	29	59	-8
				L. Medial frontal	—	-3	29	-6
				**	**	**	**	
				R. orbitofrontal cortex	10,11	12	56	-2
Wagner et al. <sup>135</sup>	Word RnTexture Rn	Texture RnWord Rn	R. superior frontal cortex	9,10	10	63	20	
			R. middle frontal cortex	46,10	24	49	6	
			L. inferior frontal cortex	44,47,45	-46	14	13	
			44	-48	28	-3		
			L. frontal operculum	47,45	-48	14	13	
	Wagner et al. <sup>135</sup>	Rn high performance	Word reading	L. superior frontal cortex	6,8	-4	14	53
				9	-13	56	26	
				9	-17	42	31	
				9	-7	49	17	
				10,11	-5	56	-9	
Wagner et al. <sup>135</sup>	Rn low performance	Word reading	L. medial frontal cortex	10	-25	49	2	
			L. middle frontal cortex	44,6	44	7	23	
			R. inferior frontal	45	48	28	14	
			R. orbitofrontal cortex	11	18	28	14	
			L. inferior frontal cortex	45	-40	35	9	
	Wagner et al. <sup>135</sup>	Reference Task	Control Task	R. anterior PFC	10/11	32	56	2
				R. dorsolateral PFC	46/9	46	35	19
				R. posterior inferior PFC	9,8,44	41	14	35
				R. frontal operculum	47	35	21	-3
				L. anterior cingulate	6,8,32	-2	21	4
TABLE 2 (continued) Study	Reference Task	Control Task	L. frontal operculum	47	-31	21	4	
			L. anterior PFC	10	-43	49	1	
			R. frontal operculum	47	36	21	-1	
			R. anterior PFC	10/11	29	56	-7	
			R. dorsolateral PFC	46,9	45	35	18	
			R. posterior inferior PFC	9,8	40	14	32	
			<b>Region</b>	<b>BA</b>	<b>x</b>	<b>y</b>	<b>z</b>	
			L. anterior cingulate	6,8,32	-2	21	41	
			L. frontal operculum	47	-30	21	3	

	Rn (0 target density)	Word reading					
Wiggs et al. <sup>136</sup> 24	Retrieving learned colors	Visual noise baseline	L. posterior inferior PFC	9,8,44	-43	14	28
	objects	uncommon to presented	R. anterior cingulate	6,8,32	2	21	37
			R. anterior PFC	10,11	26	56	-6
	Retrieving learned colors	uncommon to presented	R. frontal operculum	47	34	21	-3
			R. posterior inferior PFC	9,8	39	14	35
			R. dorsolateral PFC	46,9	44	35	18
			L. posterior inferior PFC	9,8,44	-44	14	27
			L. middle/inferior	9/45	-46	20	
			frontal cortex				
	Retrieving learned colors	uncommon to presented	L. insula		-22	16	12
L. medial premotor/anterior cingulate			6/32	-45	4	44	
R. middle frontal gyrus			9	40	14	32	

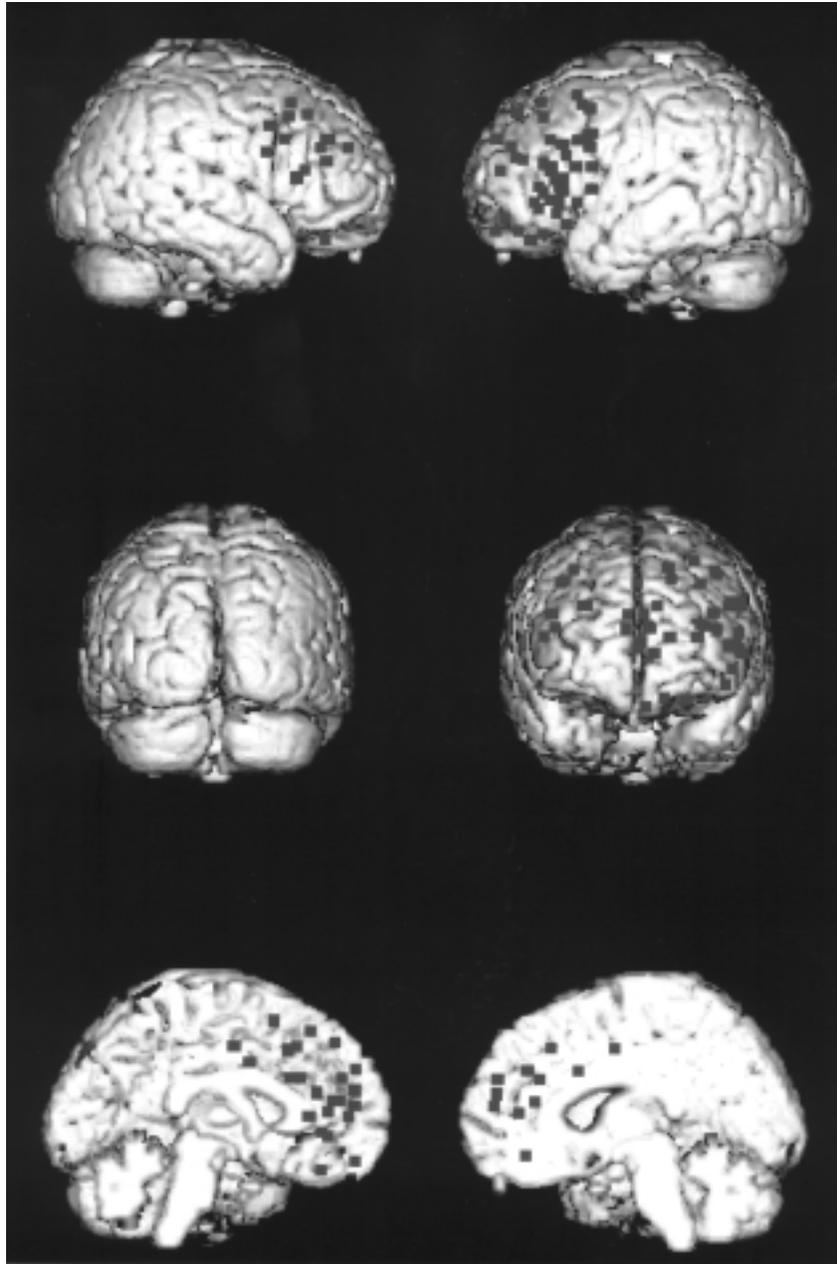
— None given.

<sup>a</sup> Talairach (1967) coordinates given.

\* Overlapping data with Shallice et al., 1994<sup>5</sup>[AU: CITE OK?]

\*\* Overlapping data with Tulving et al., 1994c [AU: NO "C" IN REFS LIST. PLEASE CONFORM]

R. = right hemisphere; L. = left hemisphere; PFC = prefrontal cortex; Rc = recall; Rn = recognition.

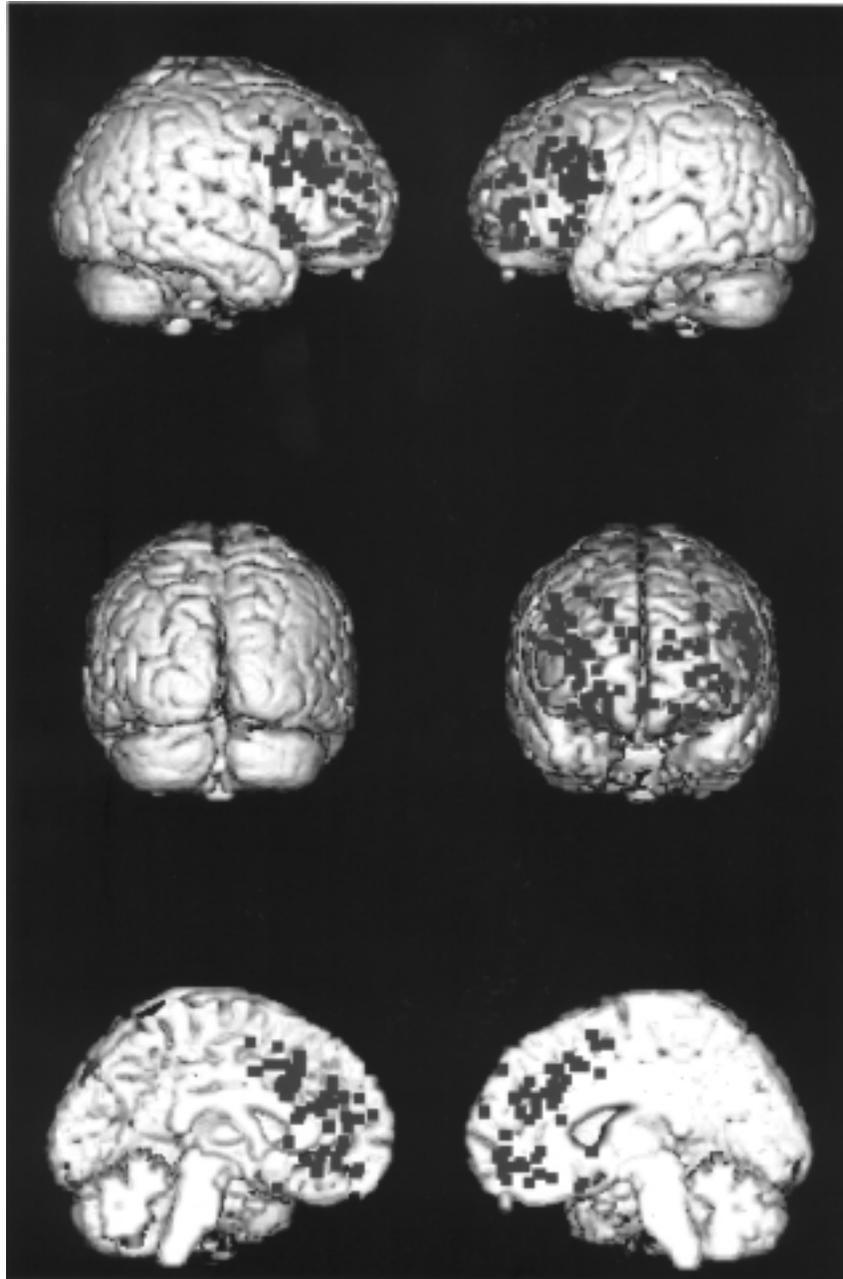


**FIGURE 1.** Schematic illustrating the distribution of activation foci reported in the studies of episodic memory encoding listed in Table 1. The red dots represent significant activation foci within the frontal lobe suggested to be associated with the *encoding* of stimuli. All of the data are plotted within standardized stereotaxic space using published coordinates where available.

to read a list of presented words during scanning. The long-term-memory condition yielded 4 peaks in the right prefrontal cortex including BA 10, 9, 46, and 47, but also a significant peak in the left prefrontal cortex (area 10). Similarly, in the short-term-memory condition significant peaks

were observed in both left and right frontal-lobe regions.

A smaller number of studies have also used nonverbal material as stimuli and reported no left or right lateral frontal-cortex activation during episodic memory retrieval.<sup>7,76</sup>



**FIGURE 2.** Schematic illustrating the distribution of activation foci reported in the studies of episodic memory retrieval listed in Table 2. The blue dots represent significant activation foci within the frontal lobe suggested to be associated with the *retrieval/recognition/recall* of stimuli. All of the data are plotted within standardized stereotaxic space using published coordinates where available.

It should be said at this point that a number of attempts have been made to reconcile such discrepant findings with the hemispheric-asymmetry model (for a discussion, see Nyberg et al.<sup>42</sup>). For example, Nyberg and colleagues<sup>42</sup> have considered the possibility that, in some cases,

during the retrieval stage of a task, encoding processes may still be active and thus may result in a continued activation of left prefrontal regions. However, such an explanation cannot adequately account for the fact that left frontal-lobe activation may still be observed during retrieval when

encoding and retrieval conditions are compared *directly*<sup>25</sup>; it is implausible that the residual left frontal-lobe activation during retrieval would actually *exceed* that observed in the same region during encoding of the same material. Andreasen et al.<sup>11</sup> have used a similar type of argument to that advanced by Nyberg and colleagues. Thus, Andreasen and colleagues suggested that the peak observed in the left prefrontal cortex during the memory-retrieval condition of that study reflected *residual* episodic memory encoding because it was stronger during the short-term-memory condition than during the long-term-memory condition. In support of this, Raichle et al.<sup>40</sup> observed that there was decreasing left prefrontal-cortex activation as subjects received more practice on a task in which they were instructed to generate related verbs in response to presented nouns.<sup>40</sup> Despite this, the suggestion by Andreasen and colleagues remains, at best, speculative because both the short-term- and the long-term-memory conditions used by those authors actually independently activated the same left anterior-frontopolar region relative to a control task. Furthermore, activation in this particular region has not been reported routinely in other studies specifically designed to study encoding processes (see Table 1).

An alternative explanation for the occurrence of left prefrontal activation during some episodic memory-retrieval tasks is that semantic, as well as episodic, retrieval processes may be active during the period that the material is being recalled. According to one version of the frontal-asymmetry model,<sup>65</sup> semantic memory retrieval, unlike episodic memory retrieval, is mediated in part by the left prefrontal cortex.<sup>65</sup> However, in this context, the distinction between semantic and episodic memory becomes vague. Unless the specific episodic and semantic components of performance can be more precisely defined in terms relating to the actual tasks that have been used in these functional-neuroimaging studies such an explanation remains unconvincing.

In general, therefore, it appears that functional-neuroimaging studies of episodic memory encoding and retrieval have failed to provide convincing support for the frontal-asymmetry model. Moreover, a number of studies have provided convincing evidence that directly contradicts the predictions of the model.

## V. DETAILED RE-EXAMINATION OF THE EVIDENCE FOR A FUNCTIONAL-ASYMMETRY MODEL

At the single-study level there are, of course, a number of investigations that do appear to support the predictions of the functional-asymmetry model. Close inspection of these results, however, suggests that in a number of cases the evidence is, at best, equivocal. For example, Kapur et al.<sup>77</sup> used PET to investigate the neural correlates of intentional learning of verbal material. Subjects were scanned twice during (1) a *reading* condition in which subjects read aloud the second of a pair of visually presented, moderately related words, and (2) an *encoding* condition in which subjects repeated the reading condition, but were specifically asked to remember the word-pairs by making meaningful associations between the two. By subtracting rCBF during the reading condition from the intentional-learning condition, 3 discrete regions were isolated in the left prefrontal cortex. These included the left anterior-inferior frontal gyrus (BA 45, 46), the left posterior-inferior frontal gyrus (BA 6, 44), and, finally, a more left *[AU: PLEASE CLARIFY. DOES THIS MEAN "FARTHER LEFT"?)* medial region centered on the anterior cingulate cortex (BA 24, 32). This study may appear to support the left-right encoding-retrieval asymmetry, but other interpretations are possible. In particular, like other studies that have focused on encoding using only verbal material, the possibility that left-hemispheric activation reflects greater involvement of language-based processes cannot be adequately discounted. Although both the reading and intentional-learning conditions used by Kapur et al.<sup>77</sup> undoubtedly involved verbal processes, these may have been greater in the latter because the subjects were actively encouraged to generate specific associations between the 2 presented words; such processes may well have involved subvocal articulation and rehearsal.

By the same token, in cases in which ostensibly nonverbal stimuli have been employed to look at episodic memory retrieval only, it is rather difficult to disambiguate the possible influences of stimulus modality and memory process on the pattern of findings reported. For example, Moscovitch et al.<sup>21</sup> presented subjects, in a prescan session, with 28 visual displays consisting of 3 line drawings of

everyday objects in unique spatial configurations. Following this, the subjects were required to carry out 1 baseline task and 2 memory tasks using different information from the displays during different scans. The baseline condition was a simple perceptual task in which subjects were presented with 2 successive displays from the original 28 and were required to indicate whether they were identical or not. The memory tasks were 2-item, forced-choice recognition tasks in which subjects were (1) presented with one of the original 28 displays paired with one that possessed the same objects, but in a different spatial configuration; or (2) one that possessed the same spatial configuration, but had one differing object. When rCBF during the perceptual task was subtracted from that during the two memory conditions, greater right prefrontal-cortex activation (BA 44, 45, 46) was observed. Although all three tasks clearly involved similar visual stimuli with comparable spatial properties, the two memory tasks undoubtedly placed greater demands on the visuospatial mechanisms that mediate recognition memory of this sort—processes that may preferentially recruit right-hemisphere regions.<sup>78</sup>

A number of other studies that, at one level, appear to support the hemispheric-asymmetry model, have used very complex experimental designs, comparing tasks that make demands on processes over and above those involved in memory encoding and retrieval. For example, Fletcher et al.<sup>17</sup> used PET to investigate both the encoding and retrieval of auditory-verbal material. In the encoding condition, 15 rare-word categories were presented, each paired with an exemplar from that same category. This procedure was repeated 3 times during a difficult distracting task and 3 times during an easy distracting task in order to control for the possible effect of automatic priming. Regional cerebral blood flow during these conditions was compared to that during a control task that required passive listening. For the retrieval of episodic-memory conditions, the subjects were prompted with a category at a regular rate during scanning and had to recall the associated exemplar. Regional cerebral blood flow was compared to that during a verbal repetition-control task. It was found that irrespective of whether the difficult or easy distractor task was used, the episodic-encoding condition, in comparison to the control con-

dition, activated the left anterior cingulate cortex extending to the left medial frontal gyrus (BA 9/10). In contrast, the episodic memory-retrieval task activated the right middle prefrontal cortex (BA 46/10) and the left anterior cingulate cortex (BA 32). Whereas these results *may* support the asymmetric involvement of left and right frontal regions in memory encoding and retrieval, other differences between the two tasks used in the encoding and retrieval conditions preclude any direct comparisons between the two sets of results. For instance, the distracting tasks that required that the subjects continually move a joystick to one of four cued positions were used during all of the encoding conditions, but not during the retrieval conditions.

Nyberg et al.<sup>79</sup> also used a rather complex design to investigate both memory encoding and retrieval within the same subjects. The participants were presented with two successive lists of words in different spatial locations during three scans and were required to encode either the words themselves, the position of the words, or whether they were presented in the first or second list. During three subsequent scans, the subjects were presented with single test words and were required to judge whether the words were old or new, previously presented on the left- or right-hand side of the screen, or previously presented in the first or second list. In general, the left middle frontal gyrus was more active during encoding, whereas the right superior frontal gyrus was more active during the retrieval condition. However, the interpretation of these results in terms of the proposed encoding-retrieval-asymmetry model is complicated by a number of factors. Specifically, the three tasks employed varied considerably with respect to their specific cognitive demands and may not have been comparable; that is, retrieval of temporal order, a core component of the list-judgment task, is likely to involve regions of the mid-dorsolateral frontal cortex.<sup>80</sup> In contrast, recognition memory or judgments of familiarity that may be sufficient for distinguishing between new and old sentences may not require the frontal lobes at all (for a review, see Petrides<sup>81</sup>). In fact, when the 3 tasks were assessed separately, no consistent pattern of frontal activations emerged; that is, none of the encoding conditions yielded task-specific frontal-activation

foci, whereas location retrieval actually yielded a significant peak in the *left* middle frontal gyrus.

In summary, therefore, even when support for an encoding-retrieval-based functional asymmetry within the frontal lobes is suggested from the results of individual studies, further consideration of the data suggests that considerable ambiguity exists. One prevailing problem is that relatively few studies have examined encoding and retrieval within the same group of subjects. Even when this approach has been employed, the encoding and retrieval tasks used often vary in ways that complicate comparisons between the two. Finally, in those few cases in which direct comparisons would seem to be appropriate, they are rarely made. For example, Haxby et al.<sup>10</sup> scanned subjects while they studied a series of faces and then tested recognition during a subsequent scan. In the recognition task, the subjects had to indicate which one of two faces was previously studied in the encoding condition. Compared to a sensorimotor-control task, the face-encoding condition was associated with an increase in activation in inferior and anterior orbital regions of the left prefrontal cortex. In contrast, the face-recognition condition was associated with increased activation in right middle and inferior prefrontal regions. Although such results suggest a double dissociation, it is important to note that the encoding and retrieval conditions were not compared *directly*. Duncan and Owen<sup>82</sup> have argued recently that, in functional-neuroimaging studies, direct comparisons between conditions assumed to make different cognitive demands may be an essential approach for understanding the functional organization of the frontal cortex. The recent functional-imaging literature is filled with proposals concerning specialized function within the prefrontal cortex although, in most cases, these claims are based on a single observed association between a particular type of behavior (or task) and activation in what appears to be a specific brain region. Comparing two experimental tasks of different cognitive demands with a common, or separate, control task is essential for examining similar and different regions of activity change. However, to conclude that any differences in activity change are specifically associated with those different cognitive demands on the basis of such comparisons is quite clearly unjustifiable. Duncan and Owen<sup>82</sup> suggest

that such overinterpretation can be avoided by direct comparisons between experimental tasks in order that two tasks can be shown to reveal different patterns of activation when compared with each other. Although extremely rare, at least one such double dissociation of frontal-lobe regions has been demonstrated recently<sup>18,19</sup> although not in the context of a left-right episodic memory encoding- and retrieval-asymmetry model. In that study, increased activation of the midventrolateral frontal cortex was observed in a condition that required subjects to retrieve previously learned category exemplars in response to a series of category names relative to a second condition that required subjects to free-recall items from a previously learned list. In contrast, greater activation in the middorsolateral frontal cortex was seen in the latter condition. Unequivocally establishing whether or not specific frontal regions, or even hemispheres, are similarly specialized for encoding and retrieval within episodic memory may also require a greater commitment to double-dissociation methodology than is currently the rule.<sup>82</sup>

It is important to stress that although the use of double dissociations is essential, the contribution of single dissociations to understanding the relationship between different cognitive functions and cortical regions should not be underestimated. In particular, in comparing two parametric experimental tasks with each other (e.g., a simple- and complex-encoding task), single dissociations can reveal which regions of activity are common to both tasks (i.e., associated with the basic process of encoding) and which regions of activity are specific to the higher-order task (i.e., associated with cognitive processes recruited by the more complex task).

## VI. THE LEFT-RIGHT EPISODIC MEMORY ENCODING AND RETRIEVAL MODEL: THE NEUROPSYCHOLOGICAL PERSPECTIVE

Although functional neuroimaging has provided a number of new techniques for examining the functions of the human brain in vivo, it is important to place the results of such studies within the wider context of neuropsychology. Owing to the recent models of episodic memory based on functional-neuroimaging results, one might rea-

sonably expect to observe dissociation of encoding and retrieval deficits in patients with left or right unilateral prefrontal-cortical excisions, respectively. This, however, does not appear to be the case; whereas most studies have shown that unilateral prefrontal patients are not disproportionately impaired at memory encoding or retrieval,<sup>51-54</sup> several others have shown that unilateral *left* prefrontal patients may even be more impaired at memory retrieval than encoding.<sup>57,83</sup>

In 1995, Wheeler et al.<sup>84</sup> investigated the relationship between frontal-lobe lesions and performance on memory-retrieval tasks through a review of neuropsychological studies carried out since 1984. Less than half these studies (44%) reported significant impairment in prefrontal-lesioned patients' performance on memory-retrieval tasks when compared to normal subjects. Moreover, within those studies reporting significant deficits, there was no evidence to support a left-right encoding-retrieval asymmetry. In contrast, left-sided frontal-lobe patients were again *more* impaired than right-sided patients on some tasks, although these tended to be those requiring verbal processes, such as word-list recall.<sup>57,83</sup> It has been suggested that the reverse pattern may be found if nonverbal stimuli are used, although existing evidence from neuropsychological studies is equivocal.<sup>83</sup> [AU: RENUMBERING OK?]

## VII. THE LEFT-RIGHT EPISODIC MEMORY ENCODING AND RETRIEVAL MODEL: CONFOUNDING EFFECTS OF MODALITY

Until recently, the possible confounding effects of stimulus modality have also been largely ignored in frontal-lobe functional-neuroimaging studies of episodic memory. Clearly, from the discussion above, the weight of evidence favors the null hypothesis that the left and right frontal lobes are *not* disproportionately involved in episodic memory-encoding and -retrieval processes, respectively. However, in generating alternative theoretical models, one important consideration given the known dominance of left-hemisphere regions for language processes<sup>78,85</sup> (for a review, see Dronkers et al.<sup>86</sup> and Walsh and Darby<sup>87</sup>; however, also see Frost et al.<sup>88</sup> and Shaywitz et al.<sup>89</sup>) is that

few studies have systematically controlled for the possible involvement of verbal processes in encoding and retrieval tasks. Subjects may use verbal strategies preferentially during the encoding of episodic information (whether that information is ostensibly verbal or not) and these strategies may be less critical for efficient retrieval.<sup>25</sup> For example, memorization of visual information is frequently accompanied by subvocal (verbal) repetition of the material to be remembered (e.g., "I see a pattern which consists of a square with round edges."). In contrast, if subjects are required to choose between two stimuli, one of which they have seen previously, verbalization is not necessarily required for visual recognition to occur. Similarly, in studies where verbal material is employed, encoding often requires the subjects to repeat and/or learn or encode a series of words, thereby emphasizing subvocal or vocal articulation and rehearsal. In contrast, retrieval of those same words, particularly when tested through free-recall, may be mediated by a combination of verbal-, semantic-, and visual-retrieval strategies. In support of this, the observation that unilateral left frontal-lesion patients may be significantly worse than unilateral right frontal-lesion patients on memory tasks has been attributed to the possibility that unilateral left frontal-lesion patients may be impaired on using verbally mediated strategies.<sup>57,83,90</sup>

A number of recent studies have investigated this issue directly and have provided evidence for an alternative model of frontal asymmetry based on stimulus or processing *modality*. For example, Owen et al.<sup>25</sup> used PET to compare encoding and retrieval of both object-locations and locations alone. A direct comparison between the rCBF changes associated with encoding object-locations and those associated with retrieving object-locations yielded results that were entirely consistent with the encoding-retrieval frontal-asymmetry model; thus, encoding object-locations disproportionately activated left frontal-lobe regions whereas retrieval disproportionately activated right frontal-lobe regions. In contrast, however, this pattern was disrupted when encoding locations alone were compared to retrieving locations alone. Our interpretation of these findings was that the pronounced asymmetry observed during the object-location memory tasks, relative to the location-memory tasks, reflects the greater

use of verbal strategies in encoding information pertaining to the relationship between an object and its location.

A logical and testable corollary of such an interpretation is that a more pronounced frontal asymmetry will be observed during memory encoding and retrieval when readily verbalizable stimuli are employed. **Three** recent functional-neuroimaging studies have investigated this hypothesis directly.

Klingberg and Roland<sup>50</sup> *[AU: IS THIS THE FIRST OF 3?]* used a paired-associate task in which computer-generated sounds were paired with abstract patterns, both of which were difficult to encode verbally. As each sound was presented, the subjects were required to choose which of two patterns was previously associated with that sound. The subjects were PET-scanned during the initial stages of this task (encoding) and also after an extensive period of training (retrieval). Only the *right* middle frontal gyrus was significantly activated during memory encoding, whereas there was no prefrontal-cortex activation at all during retrieval. This pattern of results clearly suggests that the right, rather than the left, frontal lobe may be more active during memory encoding when stimuli that are sufficiently difficult to verbalize are employed. The absence of any prefrontal-cortex activation during memory retrieval also suggests that, given extensive training, this region may not be *necessary* for memory retrieval (both error rates and reaction times were very low following training).

In another recent study, Kelley et al.<sup>91</sup> *[AU: IS THIS THE SECOND OF 3?]* compared the encoding of real words, nameable line-drawn objects, and unfamiliar faces using fMRI and found that left- and right-prefrontal regions were engaged differentially during memory encoding according to the nature of the material being remembered. During face encoding (a task classed as “difficult to verbalize”), the right dorsal frontal cortex (BA 6/44) was predominantly activated, whereas, during word encoding, the left dorsal frontal cortex (BA 6/44) was predominantly activated. During the encoding of drawn objects (“intermediately verbalizable”), bilateral dorsal-frontal activation was observed. These findings clearly suggest that the left prefrontal cortex is not necessarily involved in episodic memory encoding irrespective

of stimulus modality, as previously suggested.<sup>42</sup> *[AU: WHERE IS THE THIRD OF 3?]*

Similar results have been reported recently by a number of other studies.<sup>92-95</sup> For example, Wagner et al.<sup>92</sup> used word stimuli and abstract visual textures to demonstrate that verbal encoding and retrieval preferentially activated left inferior prefrontal regions whereas nonverbal encoding and retrieval resulted in greater right inferior prefrontal activation. More recently, Lee et al.<sup>94</sup> extended this approach to examine both encoding and retrieval, using stimuli that were formally identical during the verbal and the nonverbal tasks, varying only in the extent to which they could be processed verbally. Thus, during two PET scans, the subjects had to encode and then retrieve novel pronounceable “nonwords”; in two further conditions, they were required to encode and then retrieve the font-type in which similar stimuli were presented. When the verbal- and visual-memory tasks were compared directly, the former was associated with rCBF changes that were located predominantly in the left lateral frontal cortex, and the latter was associated with rCBF changes that were located predominantly in the right lateral frontal cortex. It is important to point out that the left-sided rCBF changes associated with the verbal conditions in this and similar studies may reflect phonological processes with no specific relationship to memory. However, such processes may be recruited routinely during many encoding tasks in order to facilitate normal memory function through mechanisms such as verbal rehearsal. Because the majority of studies have not adequately controlled such factors, any apparent left-right asymmetry of encoding and retrieval processes may be a reflection, not of discrete mnemonic processes but, rather, of the greater recruitment of verbal processes during encoding in comparison to retrieval. Accordingly, encoding and retrieval may actually involve similar regions of the lateral prefrontal cortex when all factors relating to the type of stimulus material (i.e., modality), are appropriately controlled.

## VIII. DISCUSSION

Models of episodic memory have suggested a disproportionate involvement of the left and

right prefrontal-cortical regions in the encoding and retrieval of episodic memory, respectively. According to these models, the left prefrontal cortex should be preferentially involved in the encoding of episodic memory, and the right prefrontal cortex should be preferentially involved in the retrieval of episodic memory, irrespective of the modality of the material involved.<sup>4-6</sup> As discussed in the previous two sections, the results of the current review provide no evidence to support these predictions. Thus, examination of the functional-neuroimaging data presented in Tables 1 and 2 and in Figures 1 and 2 suggests a widely distributed pattern of activation foci across *both* hemispheres during episodic memory encoding and retrieval. In addition, several studies of episodic memory encoding have reported activation in right frontal-lobe regions only, whereas many studies of encoding and retrieval have reported bilateral activation in this region.

Equally problematic for the functional-asymmetry model is the general lack of supportive evidence from neuropsychological studies of patients with focal-cortical excisions.<sup>52,54,56</sup> In fact, not only are the neuropsychological data to support any functional asymmetry equivocal at best, they also provide little evidence to support a critical role for the frontal cortex in episodic memory at all. Thus, the study by Swick and Knight,<sup>54</sup> described above, is typical of many neuropsychological investigations that have shown that patients with frontal-lobe lesions are often largely unimpaired on standard tests of episodic memory.<sup>52,56</sup> This pattern stands in stark contrast to the plethora of functional-neuroimaging studies that have reported frontal-lobe activation foci in healthy control subjects performing episodic-memory tasks. This inconsistency between the results of classic neuropsychological investigations and more recent functional-neuroimaging studies suggests that, while the frontal lobes may be actively *engaged* in many episodic-memory tasks, their integrity is not necessary for normal performance. With this in mind, it is clear that further insights about the role of human prefrontal cortex in episodic memory are likely to emerge from comparisons with studies of other types of processes assumed to be more critically dependent on the frontal lobe, such as working memory.<sup>61,67</sup>

The fundamental discrepancy between

functional-neuroimaging and clinical-neuropsychological findings also raises a more general issue of developing a theory that is sufficiently comprehensive to incorporate the main findings from both approaches and that is emancipated from a strict localizationalist perspective. In this respect, a more fruitful approach to that used previously to generate and support the models evaluated in this review might be to assume that the various processes involved in episodic memory encoding and retrieval, working memory, and related mnemonic functions are drawn from a single set of underlying components, although they may be differentially represented in different tasks (for discussion, see Duncan and Owen<sup>82</sup>). Nolde et al.<sup>64</sup> have used such an approach recently to generate a model of frontal-lobe organization based on “cortical asymmetry of reflective activity.” According to that model, basic mnemonic processes, such as temporary maintenance of remembered information or comparisons between a presented stimulus and a standard, are mediated primarily by right frontal-lobe regions. In contrast, more demanding (or reflective) mnemonic processes, such as evaluation of remembered information or self-cuing during retrieval are assumed to be mediated by left frontal-lobe regions. This hypothesis also suggests that any observed association between the left prefrontal cortex and episodic memory encoding or between the right prefrontal cortex and episodic memory retrieval is likely to reflect a difference in the (reflective) processing requirements of the encoding and retrieval tasks that have been compared, rather than encoding or retrieval, *per se*. To support the model, Nolde and colleagues compared studies of recognition, cued-recall, and free-recall classifying each experiment in terms of the level of presumed reflective demands; less “reflectively demanding” tasks preferentially activated right prefrontal regions whereas more reflectively demanding tasks activated frontal regions bilaterally. One serious confound, as the authors point out, is that those studies rated as nonreflective also tended to be those that used nonverbal materials, whereas verbal materials were used for most of the studies classed as reflective. Furthermore, a recent study by Cabeza et al.<sup>96</sup> has suggested that the left prefrontal cortex is not involved during reflective processing but, rather, is involved when generation of information is required during cued-

and free-recall tasks. In support of this, a PET study demonstrated greater left prefrontal-cortex activation during a cued-recall task in comparison to a recognition task.<sup>96</sup> Contrary to the predictions of Nolde and colleagues, increasing the task complexity did not increase activation of the left prefrontal cortex.

A more productive approach in this area, therefore, may be to focus less on the question of laterality, which invariably appears to be confounded by issues relating to stimulus modality, and more generally on the delineation and neural instantiation of the component processes of encoding and retrieval. One general theoretical framework for understanding the role played by the prefrontal cortex in mnemonic processing and its relationship to more posterior cortical-association systems is that proposed by Petrides,<sup>81</sup> based on lesion studies in the monkey. According to that model, basic memory functions, including storage and immediate processing of incoming and recalled information, are carried out within sensory-specific- and multimodal-posterior-association areas in the parietal and temporal cortices. Thus, these areas are principally concerned, not only with perceptual processing and long-term storage of information, but also with short-term retention and integration of new or recently recalled information. One obvious advantage of this model is that the frontal lobes are not *necessarily* required in all forms of memory encoding and retrieval, particularly when relatively automatic (i.e., passive) processing of information is involved. Thus, in situations that involve incidental learning or the encoding of relatively simple stimuli or short, uninterrupted retention intervals, successful retrieval may occur on the basis of stimulus familiarity alone and may require no additional higher-order memory processing. Therefore, the common observation that patients with frontal-lobe lesions can perform perfectly well on certain tasks that undoubtedly tap episodic- and working-memory processes<sup>68</sup> does not contravene the assumptions of the model. The frontal-lobes *may*, however, receive and act upon this information via (1) bidirectional connections between the posterior cortical association areas and the ventrolateral frontal cortex that, in turn, is closely connected to the middorsolateral frontal cortex, or (2) direct connections between dorsal regions of the frontal cortex and the medial tem-

poral lobe. Thus, the ventrolateral frontal cortex constitutes the first level of interaction between posterior cortical regions and the entire lateral frontal cortex. This ventral area is assumed to be critical for various first-order memory processes such as comparisons between or judgments about the occurrence or nonoccurrence of remembered stimuli. In this sense, the ventrolateral frontal cortex may trigger active low-level encoding strategies such as rehearsal, and may initiate explicit (i.e., intentional) retrieval of information from long-term memory. In the case of working memory, such retrieval would correspond to the relatively straightforward mapping of stimuli to responses such as that which is assumed to occur in spatial- and digit-span tasks,<sup>61,97</sup> or even simple delayed matching to sample paradigms.<sup>98</sup> In the case of long-term episodic memory (e.g., verbal paired-associate learning), these more active encoding and retrieval processes might correspond to the active mapping and implementation of a somewhat arbitrary learned response (e.g., a category exemplar) to a specific stimulus (e.g., a category name). Indeed, both these sets of tasks activate identical regions within the mid-ventrolateral frontal cortex.<sup>18,19,61,97</sup>

In contrast, the mid-dorsolateral frontal cortex is assumed to provide a second level of processing within memory and is recruited when active manipulation or monitoring of remembered information is required. For example, in more complex self-ordered spatial working-memory tasks that are sensitive to frontal-lobe damage<sup>61,67</sup> and activate both dorsal and ventral frontal-lobe areas,<sup>61</sup> an encoding strategy for determining the optimal sequence of choices is required that must be constantly updated or monitored during its execution (for further discussion, see Owen et al.<sup>61</sup>). In the case of episodic memory, Fletcher et al.<sup>19</sup> recently demonstrated that when subjects freely recall items from a previously learned list, activation is observed in the mid-dorsolateral frontal cortex. One key component of this episodic-memory task, like working-memory tasks that have activated the same frontal region<sup>69,99-101</sup> (for further description, see Owen<sup>102</sup>), is that each response cannot be made in isolation but, rather, can only be formed by monitoring responses made and information assimilated earlier in the trial. For example, in this case, the subject knows that

there is a specific number of items to be recalled and has to check with each new item produced that it has not been produced before.

In general, this proposed hierarchical classification of processes engaged by recall is consistent with contemporary models of human memory. For example, Baddeley<sup>103</sup> considered the relationship between working memory and retrieval from long-term memory by reviewing a number of studies that show a differential role of the phonological loop in aspects of retrieval. Thus, articulatory suppression may fail to impede relatively automatic retrieval processes in contrast to learning or encoding phases. However, while the effects of a concurrent task on retrieval accuracy are minor, measures of response latency or even performance on the secondary task itself may suffer. These effects suggest that working-memory processes are implicated more in the so-called recollection phases that include the setting-up of useful retrieval cues and the monitoring of this strategy<sup>103</sup> than in the automatic access to the memory trace envisaged in Tulving's<sup>2</sup> encoding-specificity hypothesis (for an updated view on the relationship between working-memory and retrieval-mode processing, see Shallice and Burgess<sup>104</sup>).

In neural terms, one critical aspect of this and similar contemporary models is that memory is assumed to depend upon a close functional interaction between sensory-specific and multimodal posterior-association areas and more dynamically flexible executive regions within the lateral frontal cortex. Thus, while conscious recall of remembered information may be preferentially mediated by the prefrontal cortex,<sup>81</sup> passive recognition and familiarity judgments may be accomplished by more *[AU: DOES "MORE" MEAN A DIRECTION OR A QUANTITY?]* posterior medial temporal-lobe regions. In this light, the apparent incongruity between results from brain-damaged patients and functional neuroimaging can be more clearly understood. Thus, many episodic-memory tasks can be performed adequately in a number of different ways; for example, on the basis of judgments of relative familiarity or through the active (conscious) recollection of encoded information.<sup>105,106</sup> On seeing a test stimulus, a subject may decide that it appears familiar, but be unable specifically to recall having seen the stimulus before or any information about the stimulus. Wheeler et al.<sup>84</sup> reported that

although only 8% and 50% of neuropsychological studies since 1984 demonstrated that prefrontal patients are significantly impaired on recognition and cued-recall tasks, respectively, 80% of these studies reported significant impairments in frontal-lobe patients on tests of free recall. Similarly, prefrontal patients have been shown to be impaired on tests that require memory for temporal and sequential information,<sup>53,78,107,108</sup> whereas, as we describe above, pattern-recognition memory and simple delayed matching-to-sample are relatively unaffected.<sup>68</sup> These findings suggest that, in recall, the prefrontal cortex is only essential when the retrieval of stored information is self-initiated and depends on strategies generated by the subject in the absence of external cues.<sup>57,109</sup>

While the process-specific model described above has successfully accounted for much of the working-memory literature (for review, see Owen<sup>110</sup>), it is clear that any attempt to systematically fit all of the episodic-memory studies described here into the same general theoretical framework will be compromised by differences in study design, stimulus type, methods of comparison, and data analysis. That is not to say, necessarily, that this model will not prove to be applicable to studies of episodic memory. However, before such a conclusion can be reached, systematic hypothesis-driven experiments will be required similar to those that have been used to successfully relate the model to working-memory processes in humans,<sup>97</sup> and monkeys.<sup>81,111</sup> However, it is perhaps worth noting that of the episodic-encoding tasks included in Table 1, many of those that produced predominantly ventral frontal activation involved fairly low-level mnemonic processes such as face encoding<sup>10</sup> and word-pair encoding.<sup>77</sup> In contrast, many of those tasks that produced more widespread activation involving dorsolateral frontal-lobe regions generally had more complex mnemonic requirements such as encoding temporal order,<sup>29</sup> encoding new associations between nouns and categories,<sup>30</sup> and word-list encoding with "maximal organization."<sup>18</sup> Similarly, among those studies listed in Table 2, basic retrieval processes such as short-term word recognition<sup>11</sup> and face recognition<sup>10</sup> tended to activate ventral frontal regions in the absence of significant dorsolateral involvement. In contrast, widespread activation of both ventral and dorsal frontal-lobe areas was observed during more

complex mnemonic tasks including long-term word recognition,<sup>11</sup> cued recall,<sup>14,19,26,29,112</sup> and free recall.<sup>26</sup>

## IX. CONCLUSIONS

The results of the present review suggest that laterality may not be a critical dimension for understanding the component processes of human memory, including encoding and retrieval. In short, much of the evidence to support this position remains equivocal and emerging data from recent imaging studies suggest that stimulus modality may be an important confound in this regard. Instead, it is argued that a more productive line of inquiry may be to compare the results of studies of episodic memory with those of other investigations involving tasks that are assumed to be similarly dependent on frontal-lobe mechanisms. In particular, parallels with the working-memory literature are already becoming apparent and a number of testable models have been described. Such an approach will likely enable the burgeoning data from functional-neuroimaging studies to be more readily assimilated, as well as integrated with findings from neuropsychological studies of patients and theoretical (i.e., cognitive) models of human memory.

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